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Practice review: Evidence-based quality use of corticosteroids in the palliative care of patients with advanced cancer

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Abstract

Background: It would be unusual for a patient with advanced cancer not to be prescribed corticosteroids at some stage of their disease course for a variety of specific and non-specific indications.

Aim: The aim of this practice review was to provide a pragmatic overview of the evidence supporting current practice and to identify areas in which further research is indicated.

Design: A 'state-of-the-art' review approach was used to examine the evidence supporting the use of corticosteroids for the management of cancer-related complications and in symptom control, in the context of known risks and harms to inform quality use of this medicine. We developed 'Do', 'Do not', and 'Don't know' recommendations based on current literature and identified areas for future investigation and research.

Data sources: We searched MEDLINE, EMBASE and the Cochrane library from inception to 14th October 2020. Our initial search limited to reviews, reviews of reviews, randomised controlled trials (RCTs) and controlled trials was supplemented by supporting literature as appropriate.

Results: Evidence to support common practice in the use of corticosteroids is lacking for most indications. This is in the context of strong evidence for the potential for significant toxicity and poor quality use of medicine.

Conclusion: Guidelines recommending the widespread use of corticosteroids should acknowledge the poor evidence base supporting much current dogma. Quality research is essential not only to define the role of corticosteroids in this context but to ensure good prescribing practice.

Keywords

Corticosteroids, cancer, symptom control, palliative care, evidence-based practice, review

What is already known about the topic?

- Corticosteroids are used commonly in palliative care practice for a range of indications
- Corticosteroid side-effects are common and debilitating
- The use of corticosteroids is often not consistent with the principles of quality use of medicine

What this paper adds?

- We present a 'stock-take' of the current state of the evidence in the field of corticosteroid therapy as it applies to the palliative care of patients with advanced cancer
- It provides 'Do', 'Do not', and 'Don't know' guidance and practice recommendations for clinicians regarding corticosteroid use for specific and non-specific indications
- It identifies specific research questions to direct future work.

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Implications for practice, theory or policy

- Current evidence supports the use of corticosteroids for the initial management of spinal cord compression, raised intracranial pressure, malignant bowel obstruction, lymphangitis carcinomatosis and superior vena cava obstruction.
- A short trial of corticosteroids is indicated in the management of pain and cancer-related anorexia, but the benefit if any, of corticosteroids for the palliation of other symptoms remains unknown.
- Low dose corticosteroids when used for less than 2 weeks are unlikely to be associated with toxicity (with the exception of hyperglycaemia) whereas dose-related adverse effects are common after 3–4 weeks.

Introduction

As a consequence of a range of anti-inflammatory, immunosuppressive, anti-proliferative and vasoconstrictive effects, corticosteroids are amongst the most commonly prescribed supplementary therapies used in palliative care.[1,2] However, there is little evidence-based research to guide treatment decisions with current guidelines relying predominately on expert opinion.[3]

Concerns regarding the quality use of corticosteroids, specifically relating to appropriate indications, duration of treatment, patient education and monitoring and potential risks and harms related to treatment have been raised for many years.[4,5] These concerns are particularly relevant when considering recent developments in cancer therapy leading to a prolonged survival in many patients and the earlier involvement and integration of palliative care in patient management.

Quality use of medicines when corticosteroids are used to manage symptoms, must consider not only the individual, but the clinical condition, co-existing conditions, the risks and benefits and costs for both the individual and the health system. Using medicines safely and effectively encompasses monitoring outcomes, minimising misuse and over use and improving a person's ability to solve problems related to the medication such as the negative effects of multiple medications.[6] The use of corticosteroids in palliative care is often not consistent with the principles of quality use of medicine, especially in terms of safety and effective monitoring of outcomes, minimising over-use and managing polypharmacy.

Our aim in this review was to provide a pragmatic overview of the state of the science for use of corticosteroids in advanced cancer in order to provide practical suggestions to address gaps and foster positive improvements in clinical practice and quality use of medicine.

Methods

A state-of-the-art review was undertaken using the methodology of Grant and Booth[7] to determine the extent and characteristics of the evidence supporting the use of corticosteroids in palliative care. State of the art reviews address more current matters to offer new perspectives on issues and to identify gaps in the literature for further investigation and research.[7] The literature search was modelled on rapid review methodology,[8] where an initial search was limited to reviews, reviews of reviews, RCTs and controlled trials. An additional search of existing guidelines or other relevant literature was then conducted if indicated following the initial search. The final search of MEDLINE (EBSCO) and EMBASE (Embase.com) was conducted on 14th October 2020. Controlled vocabulary (thesauri terms/subject headings such as MeSH or EMTREE) in combination with free text words in the title and abstract was used to identify relevant literature within the databases, based on a list of corticosteroids used in palliative care, as well as synonyms based on palliative care, end of life and advanced cancer. In order to provide a realistic view of the 'state of the science' in palliative care practice, all literature considered relevant by the expert panel was considered. The search strategies are shown in Supplemental Material 1. The Cochrane Database of independent reviews was independently screened. The search was limited to English language papers, but not by publication date. It focused on adults with cancer but supportive evidence from other areas and medical specialties were included if appropriate. The most recent systematic review of a topic was generally used rather than source trials. We have also considered guidelines when referring to expert consensus. For the purpose of this practice review, 'short term' is defined as less than 2 weeks (on the basis of toxicity data) and 'long term' as greater than 4 weeks (based on NICE guidance).[9] We have not included any recommendations regarding the use of corticosteroids for anticancer treatment.

Independent screening was conducted by two researchers, and 37 articles were identified as relevant to this review. Methods were compliant with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.[10,11] A critical appraisal of included sources of evidence was undertaken using the Mixed Methods Appraisal Tool (MMAT) for RCTs and cohort studies.[12] The quality of included evidence was considered by all authors when reaching consensus and defining the strength of recommendations (Table 1).

We constructed this practice review by utilising the D3 (Do's, Don'ts and Don't Know's) method, where key themes are identified and practice recommendations made and graded based on the D3 approach (Table 2).[13] 'Do' and 'Do not' practice recommendations were made

Table 2. How categories of recommendation were decided.

Do	Evidence for effectiveness in palliation in cancer patients AND a clear favourable benefit to risk ratio
Don't	Evidence of lack of efficacy in palliation of cancer patients AND/OR a clear unfavourable benefit to risk ratio
Don't know	Limited evidence of effectiveness in advanced cancer and further research is required AND/OR High-quality published data to support use but in a context other than cancer
Strength of recommendations	
Strong	Large and consistent body of high quality evidence such as a systematic review or meta-analysis of randomised controlled trials
Moderate	Solid empiric evidence from at least one controlled trial or consistent findings from cohort studies plus consensus of the review authors following critical appraisal of the evidence
Tentative	Limited empiric evidence but consensus opinion from experts plus consensus of the review authors following critical appraisal of the evidence

when empiric evidence exists, if necessary, using supportive evidence from other medical specialties or consistent expert consensus. 'Do' and 'Do not' recommendations are graded as strong, moderate or tentative according to the quality, consistency and size of the evidence to support each recommendation. 'Don't know' recommendations were made where there was an absence of evidence or lack of consensus in the evidence to support the use of corticosteroids in a particular context, or a quality systematic review that identifies a knowledge gap. Specific research questions were raised as a consequence to direct future work. The publications under-pinning the strengths of recommendation for each item are listed separately in a supplementary file (Supplemental Material 2).

Practice recommendations

Complications of advanced cancer

Do's

Raised intracranial pressure. Corticosteroids are indicated for the palliation of symptoms (headache, nausea, neurological impairment) of raised intracranial pressure[14] and in the initial management of spinal cord compression.[15] Optimal starting doses are controversial. A randomised study[16] of patients with brain metastases found 4 mg to be as good as 16 mg over 4 weeks with respect to performance status. There is no clear guidance regarding dose tapering. A randomised, controlled study of whole brain radiotherapy plus dexamethasone versus optimal supportive care (including dexamethasone) in lung cancer patients with brain metastases showed no difference in overall survival, dexamethasone use or quality of life between the two groups.[17]

Spinal cord compression. In spinal cord compression, no difference in pain, ambulation or bladder function was seen after 24 h irrespective of whether the patient received 100 mg or 10 mg iv dexamethasone.[18] Despite being entrenched in everyday practice, a Cochrane review was unable to determine whether high doses of corticosteroids offer any benefit over moderate doses or no doses with respect to enhancing ambulation, survival, pain reduction or urinary incontinence.[19] Lower dose regimens are associated with fewer complications.[20]

Bowel obstruction. Corticosteroids are used routinely in the conservative management of bowel obstruction to speed resolution despite only moderate evidence from two underpowered studies.[21]

Other specific indications. Similarly, there is very low level evidence to support the established practice of using steroids to palliate symptoms of lymphangitis carcinomatosis, superior vena cava and large airway obstruction.[22]

Don'ts

Uncertain diagnosis. Dexamethasone induces apoptosis of B cells, including monoclonal cells and ALL cells. Therefore, steroids can obscure the histopathological picture of lymphoma and complicate and delay the diagnostic process.[23] Pre-treatment with steroids prior to diagnosis should therefore be avoided unless essential to avoid major morbidity (e.g. compromised airway) and/or in those patients in whom a specific diagnosis is not to be sought. NICE guidance state that the prescription of steroids is contraindicated in patients who present with spinal cord compression where there is a significant suspicion of lymphoma.[24] These concerns have been disputed in the case of primary CNS lymphomas.[25]

Don't knows. Our search did not identify any controlled studies on the use of corticosteroids for the palliation of symptoms associated with liver metastases or obstructive lymphadenopathy.[26] A systematic review could find no controlled study of any agent used for the palliation of bronchorrhea.[27]

Table 1. Summary of guidelines for the use of corticosteroids in palliative care.

1.	Complications of advanced cancer	Strength of recommendation
Do's	i. Corticosteroids are indicated in the management of spinal cord compression	Moderate
	ii. Corticosteroids are effective in the initial management of headache, nausea/vomiting and neurological abnormalities associated with raised intracranial pressure from brain metastases	Strong
	iii. A trial of corticosteroids is warranted to speed the resolution of malignant bowel obstruction	Tentative
	iv. Corticosteroids are indicated to palliate dyspnoea associated with lymphangitis carcinomatosis	Tentative
	v. Corticosteroids should be used in the initial management of complications (dyspnoea, oedema, head fullness, chest pain) associated with superior vena cava obstruction	Tentative
Don'ts	vi. Prescribe corticosteroids to patients presenting with a mass lesion if there is a high suspicion of lymphoma unless clinically imperative	Tentative
Don't knows	vii. Are corticosteroids effective in the palliation of nausea and anorexia associated with liver metastases?	–
	viii. Can corticosteroids be used to reduce oedema/swelling associated with obstructive lymphadenopathy?	–
	ix. Do corticosteroids improve bronchorrhoea?	–
2.	**Symptom control**	**Strength of recommendation**
Do's	i. Use corticosteroids to improve appetite in the short term (<2 weeks)	Tentative
	ii. A trial of corticosteroids is indicated in the management of pain	Tentative
Don'ts	iii. Corticosteroids should not be prescribed in the absence of a clearly defined symptom improvement goal	Tentative
Don't knows	iv. Are corticosteroids effective in the treatment of nausea and vomiting not associated with anti-cancer therapy?	–
	v. Do corticosteroids improve mood?	–
	vi. Is a trial of corticosteroids indicated to improve fatigue?	–
	vii. Is a trial of corticosteroids indicated for the palliation of dyspnoea?	–
	viii. Do steroids relieve cough related to cancer?	–
	ix. Do corticosteroids improve Quality of Life?	–
	x. Do corticosteroids lead to better patient outcomes in terminal care?	–
3.	**Potential risks and harms**	**Strength of recommendation**
Do's	i. Use corticosteroids for shortest possible time periods to avoid toxicity	Strong
	ii. Use lowest effective dose (that which results in symptom improvement) to avoid toxicity	Strong
	iii. Use prophylactic proton pump inhibitors or histamine H2 receptor antagonists to avoid gastric toxicity when corticosteroids are prescribed for more than 2 weeks	Tentative
	iv. Monitor patients closely for the development of oral candidiasis	Moderate
	v. Recognise that steroid-induced hyperglycaemia is common and of rapid onset	Strong
Don'ts	vi. Prescribe long term steroids without regular review of adverse effects	Strong
	vii. Use high dose corticosteroids (>12 mg dexamethasone) in those with a prior history of neuropsychiatric illness	Moderate

(Continued)

Table 1. (Continued)

3.	Potential risks and harms	Strength of recommendation
Don't knows	viii. Do short term (<2 weeks) corticosteroid 'bursts' reduce toxicity?	–
	ix. Is it possible to reverse the side effects of corticosteroids after discontinuation of therapy?	–
	x. Does switching to a less potent corticosteroid reduce adverse effects?	–
	xi. Are supplementary calcium/vitamin D and bisphosphonates indicated in this population to avoid complications of reduced BMD in patients on long term (>1 month) steroid therapy?	–
	xii. Is prophylactic antifungal therapy indicated in patients receiving palliative care?	–
	xiii. Are prophylactic antibiotics (trimethoprim-sulphamethoxazole or equivalent) indicated in those patients with advanced cancer likely to be on long term (>1 month) corticosteroids?	–
4.	**Quality use of medicines**	**Strength of recommendation**
Do's	i. Clearly document reason for prescribing steroids	Moderate
	ii. Provide adequate patient education to all patients starting corticosteroids	Strong
	iii. Monitor long-term corticosteroid use for adverse events and efficacy	Moderate
	iv. Dose once-twice daily (not 3–4 times daily)	Strong
	v. Limit treatment to <2 weeks in the absence of benefit to avoid toxicity	Moderate
	vi. Take a full medication history and recognise potential drug interactions	Moderate
Don'ts	vii. Commence corticosteroids with no plan to monitor or reduce if no benefit	Strong
	viii. Prescribe steroids without a prior assessment of risk (e.g. prior adverse event, infection, wound healing, gastric irritation)	Tentative
	ix. Fail to monitor blood glucose levels in all patients when first started on corticosteroids	Strong
	x. Stop steroids abruptly in patients who have been taking more than 4 mg dexamethasone (or equivalent) for more than 5 days	Strong
Don't knows	xi. Is dexamethasone the corticosteroid of choice for all indications?	–
	xii. Is the same starting dose of corticosteroid indicated irrespective of condition?	–
	xiii. What is the optimal weaning regimen of dexamethasone?	–
	xiv. Is the optimal weaning dose the same for all patients and all indications?	–
	xv. Is short burst treatment as effective as longer continuous courses for the palliation of symptoms?	–
	xvi. Does a morning dose of dexamethasone protect against sleep disturbance?	–
	xvii. What is the optimal regimen when using insulin (or other hypoglycaemic agents) in the treatment of corticosteroid-related hyperglycaemia?	–
	xviii. Should patients on long term corticosteroids entering the dying phase continue corticosteroids via the subcutaneous route?	–

Symptom control

Do's

Appetite. The conclusion of a systematic review published in 2014 that included eight trials (controlled studies and case series) was that steroids are beneficial in treating anorexia associated with malignancy.[28] Two RCTs published since that time however[29,30] show improved appetite with dexamethasone, megestrol acetate and placebo[29] with no difference between arms and more toxicity in the participants randomised to steroids. Recent ASCO guidelines state that in the absence of robust evidence, clinicians may choose not to prescribe medications for cachexia but that a trial of short term corticosteroids might be considered.[31]

Pain. Similarly, the evidence for the efficacy of corticosteroids in pain management is marginal but warrants a therapeutic trial.[32] Significant short-term pain relief was noted in some of the studies included. Despite this relatively weak evidence, in a large survey of American palliative care providers, 98% of responders reported having prescribed corticosteroids as adjuvant pain therapy.[33] A recent review[34] has confirmed the finding that dexamethasone reduces pain flare post radiotherapy.

Don'ts. There is little justification for prescribing corticosteroids unless targeting a clearly defined problem or symptom and closely monitoring the outcome.

Don't knows

Nausea/vomiting. Despite evidence supporting the use of steroids to prevent nausea/vomiting associated with chemotherapy,[35] a recent Cochrane review concluded that the evidence for the efficacy of corticosteroids for the control of non-treatment related nausea and vomiting is weak.[36]

Mood. One randomised trial assessing mood (anxiety, depression and wellbeing) as a secondary outcome[37] found dexamethasone to have no benefit over placebo at days 8 or 15.

Fatigue. Although some RCTs have reported benefit in fatigue,[37–40] the conclusion of the most recent systematic review of steroids in patients with cancer or stem cell transplantation[41] is that steroids are not effective. Mücke et al.[42] was only able to identify two studies with a focus on corticosteroids and fatigue as the primary outcome in a systematic review of pharmacological agents used for fatigue. Thiem et al.[43] report inconsistent results for fatigue and weakness and no improvement in tiredness or energy in a review that included both controlled and uncontrolled studies.

Dyspnoea. Similarly, a Cochrane review of corticosteroids for cancer-related breathlessness[44] recommended caution in prescribing of steroids. The few studies included were of high risk of bias and could neither support not refute corticosteroid use for this indication.

Cough. UK guidelines for lung cancer recommend steroids for those patients with cough not responding to simple linctus. This practice is based on a systematic review of non-cancer respiratory disease (mainly asthma and COPD).[45,46] Whether it can be extrapolated to cancer is unknown.

Quality of life (QoL). QoL has been assessed as a secondary outcome measure in several RCTs.[29,30,37,39,40,47,48] Most studies in a systematic review by Thiem et al.[43] of steroids in tiredness and weakness showed an improvement in QoL. However, in a prospective study of patients receiving dexamethasone along with radiotherapy,[49] in which QoL was followed over time as a primary outcome measure, no consistently significant differences in QoL were observed.

Terminal care. Several older studies reported benefit when steroids are used in terminal care.[48,50,51] The authors variously describe improved comfort, well-being and QoL but the studies are all heterogeneous with significant risk of bias.

Risk and harms

The extensive side-effect profile of corticosteroids and the mechanisms involved are well described.[52] A meta-analysis[53] documents an increased incidence of peptic ulcer, dermatological effects, hyperglycaemia, hypertension and psychosis in patients on steroids and a non-significant increase in sepsis, osteoporosis and tuberculosis. The most common symptoms recognised in a retrospective review were hyperglycaemia, oedema, psychiatric disturbance and Cushing's syndrome.[54] Approximately 10% of patients are said to develop proximal myopathy. In a case series, this was more common in the elderly and after prolonged use.[55] In a large patient survey of patients with non-malignant lung disease, patients on corticosteroids reported significantly more fractures, cataracts, use of antacids, muscle weakness, back pain, bruising and oral thrush.[56] The adverse effects of corticosteroids are poorly reported in most studies.[57]

Do's

Duration of use. The literature is consistent in stating that short-term steroid use ($<$2 weeks) is not generally associated with toxicity.[37–39,47] Conversely, side-effects increase over time.[52,54] A meta-analysis of bone mineral density (BMD) studies found the risk of fracture to increase rapidly within 3–6 months of corticosteroid treatment.[58]

Dose. Several studies of the use of steroids for the palliation of brain metastases have pointed to the relationship between dose and toxicity. Toxicity was more frequent at

16 mg than at 4 mg when treating metastatic brain disease.[13] This is consistent with a review plus survey[59] undertaken in patients with brain metastases in which the most common side-effects (weight gain, insomnia, gastrointestinal symptoms, proximal muscle weakness and psychiatric disturbance) were more frequent at doses above 16 mg/day. In the setting of brain metastases, higher doses give more toxicity and not necessarily better results.[60] Significantly more serious adverse events were reported by patients receiving high dose steroids (96 mg) compared 16 mg for treatment of spinal cord compression.[19,61] There is a strong correlation between cumulative dose and loss of bone mineral density (hence risk of fracture).[58] In a prospective study of patients on dexamethasone receiving brain radiotherapy, at 2 weeks post, patients on higher doses of dexamethasone had worse physical and emotional functioning and scored worse dyspnoea and fatigue.[49]

Gastric protectants. Prophylactic proton pump inhibitors or histamine H2 receptor antagonists are often prescribed regardless of guidelines suggesting otherwise.[62] Peptic ulcer was shown to be a rare complication of corticosteroid therapy in a meta-analysis of all RCTs in which steroids had been administered.[53] Subsequent reviews have reported an incidence of gastrointestinal complications of less than 8%.[54,59,63] These data do not necessarily include symptoms such as gastric irritation or reflux. The risk/benefit ratio and lack of evidence of short-term toxicity have led the authors to support the use of proton pump inhibitors or equivalent in those prescribed corticosteroids for more than 2 weeks.

Fungal infections. The results of a large questionnaire survey of patients taking corticosteroids for non-malignant lung disease (asthma, COPD, etc.) was compared to matched controls. Significantly more oral candidiasis was reported by patients taking steroids.[56] In a large prospective survey of cancer patients on steroids, approximately one-third developed oral candidiasis.[64]

Hyperglycaemia. Two RCTs[29,47] have documented a higher incidence of hyperglycaemia in patients randomised to corticosteroids. In a prospective audit of non-diabetic patients treated with 'high dose' steroids (prednisone $>$25 mg or dexamethasone $>$4 mg/day), over 80% had at least one blood glucose recording of $>$8 mmol/L and 70% at least one over 10 mmol/L.[65] Hyperglycaemia develops very rapidly (within 48 h).[65] A retrospective review suggests a dose relationship.[66]

Don'ts

Failure to monitor. There is consensus that the incidence of adverse events is associated with dose and duration of corticosteroid therapy.[54,67] The corollary from this is that all patients prescribed corticosteroids for longer than 14 days must be monitored for toxicity.

Prior neuropsychiatric disorders. Neuropsychiatric adverse effects attributed to corticosteroids include anxiety, depression, delirium, sleep disturbance, suicidal ideation, impaired memory and concentration, mania and psychosis.[68] The incidence of any of these amongst a large epidemiologic study of over 350,000 primary care patients was 22.2 per 100 person-years at risk for first-course treatments.[69] Those treated with high doses ($>$80 mg prednisone/day) or with a previous history of neuropsychiatric disorder were at greater risk.

Don't knows

Steroid 'bursts'. No study to date has assessed the benefit of short-term steroid 'bursts' in reducing toxicity whilst maintaining benefit.

Side-effects reverse after discontinuation of steroids. This statement is based on expert opinion alone,[70] except for loss of BMD that has been shown to be reversible in a meta-analysis.[58]

Switching to a less potent corticosteroid. Few studies other than case reports have compared the incidence of adverse events after switching to another steroid.[67] A retrospective case review suggests that rotation from dexamethasone to prednisone or hydrocortisone may be beneficial in reducing proximal myyopathy.[55] Another randomised cross-over study states that antiemetic corticosteroid rotation from dexamethasone to methylprednisolone prevents dexamethasone-induced hiccup.[71]

Bone mineral density. More than 10% of patients who receive long term ($>$3 months) steroid treatment will have a fracture and 30%–40% with have a vertebral fracture.[72] Larger cumulative doses also seem associated with an increased risk of developing osteoporosis.[67] A Cochrane review supports the use of bisphosphonates to reduce risk of vertebral fractures and the prevention and treatment of steroid-induced bone loss.[73] Recommendations regarding treatment with calcium and vitamin D and/or bisphosphonates depend on a number of factors (e.g. age, gender, previous fracture),[72] and may not always apply to patients with advanced cancer and a limited life expectancy.

Prophylactic antifungals. A systematic review documents an increased risk of oral candidiasis during cancer therapy but does not specifically mention steroids. In these patients, the weighted prevalence of oral fungal infections in those patients given prophylactic antifungals was less than that in patients on placebo. Systemic antifungals were more efficacious than topical therapy.[74] Although it is well established that patients on corticosteroids are at risk of developing fungal infections, it is not known whether prophylactic systemic antifungals are of benefit in the palliative care population.

Prophylactic antibiotics for PJP. Prolonged administration of corticosteroids is the most common setting in which patients develop *Pneumocystis jirovecii* (PJP).[75] It has been recommended that patients with cancer-related immunosuppression who are receiving corticosteroids at a dose ⩾20 mg prednisone equivalents (⩾3 mg dexamethasone) daily for ⩾1 month should receive prophylaxis against PJP.[76] In a Cochrane review, the incidence of PJP in patients given trimethoprim-sulphamethoxazole (or equivalent) was reduced by 85%. Most of the patients included in the review had acute leukaemia or had undergone an organ or bone marrow transplantation.[77] As above, it is not clear whether these recommendations should be extrapolated to a palliative care population.

Quality use of medicines

Do's

Documentation. Repeated surveys have pointed to the poor documentation of corticosteroid prescribing.[4,78] Although there is no evidence that proper documentation improves patient outcomes, expert opinion strongly favours this recommendation. Some have advocated for the use of a 'steroid window' or alert in online notes to trigger regular review.

Patient education. Considering the significant toxicity of corticosteroids, the authors advocate for the provision of written information to be given to all patients prescribed steroids. This should include information regarding all possible toxicities as well as a dose tapering schedule.[79]

Monitoring. Again, considering the significant toxicity of corticosteroids, expert consensus is that systems should be put in place to ensure that all patients commenced on steroids are monitored for toxicity and efficacy. This has been attempted in a primary care setting with some success.[80] A corticosteroid specific questionnaire, the Dexamethasone Symptom Questionnaire (DSQ) has been validated for this purpose.[49,81–84] The TRIGGER-CHRON is a trigger tool used to detect adverse events associated with high-alert medications.[85] This tool identified corticosteroids as the high-alert medication most commonly associated with adverse events in patients with multimorbidity.

Dose once-twice daily. This is implied from pharmacokinetic data confirming the long half-life and duration of action of dexamethasone.[86] There is only anecdotal evidence to support the practice of morning dosing over morning/night dosing however.

Limit treatment to 14 days in the absence of benefit to avoid toxicity. This guidance is supported by the short-term toxicity data (see above).

Potential drug interactions. Medicines that induce hepatic enzyme cytochrome P-450 isozyme 3A4 may increase the metabolism and thus reduce the effects of corticosteroids. Medicines that inhibit hepatic enzyme cytochrome P-450 isozyme 3A4 may decrease glucocorticoid clearance. Antithyroid agents, oestrogens and other oral contraceptives may decrease hepatic metabolism and thus increase the effects of corticosteroids. Concurrent administration of dexamethasone with anticoagulants, heparin, streptokinase, urokinase, alcohol or non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin may increase the risk of gastrointestinal ulceration or haemorrhage.[87] The potential for dexamethasone interaction with antiviral agents is well established. There is good evidence for potential interactions with live vaccines, some antifungal agents and various enzyme inhibitors.[87]

Don'ts

Commence corticosteroids with no plan to monitor. This guidance is supported by the toxicity data (see above).

Fail to monitor blood glucose levels in all patients. As documented above, there is high-quality evidence of an increased incidence of hyperglycaemia in patients on corticosteroids that can develop within a few days.[29,47] The symptoms associated with hyperglycaemia can cause significant morbidity.

Stop abruptly. Adrenal suppression following exogenous steroid use is dependent on multiple factors (specific corticosteroid, dose, duration and route of administration) but can occur at any dose above 5–7.5 mg prednisone/day (around 1 mg dexamethasone/day).[88,89] Sudden withdrawal of prolonged or 'high dose' steroid therapy may result serious morbidity (fatigue, weakness, arthralgias, nausea, hypotension).[90] Corticosteroids should not be stopped abruptly in patients who have been taking more than 4 mg dexamethasone (or equivalent) for more than 5 days. There are no definitive guidelines with respect to the reduction and stopping of steroids even after long-term use.[91]

Don't knows

Corticosteroid of choice. Dexamethasone is used as the steroid of choice in palliative care because of its long half-life, glucocorticoid potency and low mineralocorticoid activity. There are no studies confirming that this drug leads to superior outcomes for patients and other medical specialties favour other steroids such as prednisone.

Starting doses. There is no research to guide starting doses. The choice of starting dose remains arbitrary and differs according to the indication.[5,92]

Weaning regimens. Similarly, there are no evidence based weaning protocols and considerable variation in practice.[91,93] A stepladder guideline based on symptom severity has been proposed for patients with primary and metastatic brain tumours.[94] Others have suggested an algorithm approach[92] and/or individualised treatment regimens based on clinical tolerance.[16]

Short burst treatment is as effective as longer courses. There is no research to support or refute this statement.

Sleep disturbance. Several studies describe sleep disturbance in patients on steroids.[49,95] A prospective observational study reports an incidence of sleep disturbance at about 20%. The deleterious effect of corticosteroids on sleep quality has been shown to be dose related[49,96]and may be time related in that patients on twice daily methylprednisolone for 14 days had no more sleep disturbance than those on placebo.[97] Most guidelines recommend giving steroids early in the day to prevent this, consistent with the physiological circadian rhythm of endogenous adrenal glucocorticoids. Morning once daily administration is said to minimise hypothalamic-pituitary-adrenal axis suppression.[98] However, there is no controlled sleep study to show that morning dosing reduces insomnia and pharmacokinetic studies suggest this is unlikely considering the long biological half-life of the drug (36–54 h).[86]

Treatment of choice for corticosteroid-induced hyperglycaemia. The lack of quality studies, consistent target glucose levels and glucose monitoring, render identification of optimal pharmacological interventions for glycaemic control difficult.[99] Guidance on the management of corticosteroid-related hyperglycaemia is based on expert opinion alone.[100]

Steroids at end of life. Some withhold steroids once a patient is no longer responsive. Others continue low dose dexamethasone via the subcutaneous route in an attempt to reduce morbidity associated with steroid withdrawal.

Limitations

This practice review covers a broad range of topics and was undertaken using a mixed method scoping review methodology of the cancer and palliative care literature. A formal systematic review of each topic was not undertaken. Evidence from other medical specialties (e.g. rheumatology or respiratory medicine) was used when necessary but a full search of all topics across all medical fields was not undertaken. It is not always appropriate to translate evidence from other specialties that use corticosteroids in a different manner or for much longer time periods than is typical in palliative care. Our search focused on RCTs and systematic reviews which may not be appropriate when investigating quality use of medicine. The quality of papers included within published systemic reviews was not re-examined.

Summary

Despite the fact that corticosteroids are so widely used in palliative care, the evidence of benefit in most situations is disappointingly sparse. As a consequence, there is considerable variation in the use of corticosteroids in practice,[101] a lack of certainty regarding appropriate indications and insufficient evidence to recommend one corticosteroid over another, a starting dose, regimen or weaning dose. High quality trials are needed to evaluate the safety and effectiveness of corticosteroids for the palliation of most symptoms associated with advanced cancer. This is of particular concern in that the toxicity of these drugs is so well described. It is unlikely that much of the necessary evidence will ever be obtained because of the widespread belief of effectiveness of corticosteroids over a range of indications. More emphasis must be placed on the quality use of corticosteroids, including the provision of patient information, the monitoring of long term use, the identification of potential drug interactions and the limitation of treatment to short time periods in the absence of benefit.

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Author contributions

This was a solicited review. J.H. led the project and co-ordinated the consensus meetings. K.R. undertook the literature searches. A.H. was primarily responsible for managing the end-note file and input on quality use of medicine. All authors contributed to the content, contributed to the consensus reviews, reviewed drafts and approved the final document.

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Supplemental material

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